with "diabetes".

Claim 16 has not been canceled because claim 1 has been amended to also cover SLE, as justified by page 37, line 4 of the specification and section 4 of the July 8, 1994 Classen declaration. However, claim 16 has been amended to avoid referring to "disorder".

2. Enablement

2.1 At the outset, it must be stated that the §112, para. 1 rejection is improper in that it conmingles utility/operability issues with "pure" enablement issues. The Examiner did not make a joint §101/§112 para. 1 "lack of utility" rejection complying with the utility Examination Guidelines, and a separate "pure enablement" rejection under 112 para. 1, as required by MPEP §2164.07(a)(1); 2107(d). In view of Examiner's failure to comply with these requirements, and the attendant confusion, applicants will oppose any attempt to make the next action "final".

At page 3 of the office action, the PTO states that "it is not predictable that the animal data disclosed in Examples 1-3, would be directly extendable to other mammals". This appears to be a contention that the invention lacks utility in mammals other than mice. According to MPEP §2164.07, "Office personnel should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a lack of utility basis unless a 35 U.S.C. 101 rejection is proper. In particular, the factual showing needed to impose a rejection under 35 U.S.C. 101 must be provided if a 35 U.S.C. 112, first paragraph [rejection] is to be imposed on 'lack of utility' grounds."[2]

---

[2] It is particularly surprising that the Examiner has failed to follow these instructions, given that on November 6, 1995, in his "Second Supplemental Response", Applicants called the Examiner's attention to the Final Utility Examination Guidelines, which required that the §101 standard be applied to a "lack of utility" rejection under §112, para. 1.

Dr. Classen's application asserts that early administration of immunogens to mammals can reduce the incidence of diabetes later in life. That is plainly a "practical utility" within the meaning of 35 U.S.C. §101. That assertion cannot be simply dismissed as wrong. Rather, the Examiner "must determine whether the assertion is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided)". See MPEP §2107.01(b)(ii). Sound reasons must be articulated which explain why a person of ordinary skill would conclude that "it is more likely than not that an asserted utility is not credible". Clearly, what is required is a plausible utility, not a proven one.

Moreover, the rejection must be specific, in particular, it must explain why any in vitro or in vivo data supplied by the applicant would not be reasonably predictive of an asserted therapeutic utility from the perspective of a person of ordinary skill in the art. MPEP §2107.02(c).

Finally, a §101 rejection must have evidentiary support that justifies questioning the operability of the invention. "Documentary evidence...can and should be cited...." See MPEP §2107.01(c).

The sole reasoning supporting the Examiner's refusal to accept extrapolation from the animal data is that "each mammal has a particular rate of development, particular responses to immunogens, and susceptibilizes to disease, and times and types of immunization would be predicted to have widely varying affects [sic] on any particular mammal." The Examiner does not rely on any specific data relating to the treatment of diabetes, to differences in immune system maturation between mice and other mammals, or to the particular immunogens employed. It is essentially a "boilerplate" remark that it could be applied to

any drug, for treating any disease, that had been tested in only one species of mammal.

MPEP §2107.02(c) specifically states that "data generated using in vitro assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility". It is well settled that animal data (or even in vitro data) can establish the utility of a therapeutic method in humans if there is an accepted correlation between efficacy in the animal in question, and efficacy in humans. See In re Jolles, 206 USPQ 885 (CCPA 1980); Nelson v. Bowley, 206 USPQ 881 (CCPA 1980); Cross v. Iizuka, 224 USPQ 739 (Fed. Cir. 1985). The law does not requires that this correlation be perfect, merely that it give the researcher a reasonable expectation that a drug which does well in animal testing will be successful in humans.

The expectation exists here because:

(1) the specification establishes efficacy in NOD mice, and NOD mice are an accepted animal model of diabetes mellitus in humans;

(2) the method of the present invention was effective in a second species of animals, BB rats, which are likewise accepted as animal models of human diabetes mellitus; and

(3) the utility of the present invention in humans is made more believable by human epidemiological data.

It is now widely accepted by those skilled in the art that type I diabetes in humans responds similarly to immune intervention as does diabetes in NOD mice and BB rats. Diabetes in all three species is considered to be an autoimmune disease based on the presence of islet cell autoantibodies and strong genetic linkage between the development of diabetes and MHC genes (New England Journal of Medicine 314:1360-1368,1986; Diabetes Reviews 1:15-42,1993). Immunological events occurring in the

first 2 months of life have been clearly shown to be responsible for the development of diabetes in NOD mice and BB rats. Similarly, recent human epidemiology data shows that immunological events occurring at birth have a profound effect on the development of human diabetes. These events include maternal fetal blood group incompatibility as well as exposure to rubella virus and nitrates at birth (Diabetes Reviews 1:15-42,1993; Diabetologia 35:671-765,1992).

Clinical trials have shown that type I diabetes in humans can be prevented by immunosuppressants like cyclosporine when administered to prediabetics or newly diagnosed diabetics (Diabetes Reviews 1:15-42,1993). Immunosuppressants have a similar effect on NOD mice and BB rats (Clinical and Investigative Medicine 10:488-495,1987). The NIH recently embarked on a trial of screening up to 80,000 children to initiate a program of treating prediabetics with insulin immunotherapy, after a small phase I trial in humans supported results developed in NOD mice (Lancet 341:927-928,1993).

Detailed supporting citations are set forth on pages 5-8 of the July 8, 1994 Amendment. These citations establish that there is a reasonable correlation between efficacy in NOD mice (or BB rats) and efficacy in humans.

MPEP §2107.02(d) states that "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials." Nonetheless, Applicant has supplied human epidemiological data supporting his assertion of utility. This data revealed that standard childhood immunizations (i.e., later than when taught herein) against infectious disease increased the incidence of diabetes. It also indicated that early immunization with BCG and smallpox reduced the incidence of diabetes (although this effect was not recognized prior to the instant invention).

2.2 The Examiner asserts that there is "no guidance in the specification regarding types of immunogens, amounts of immunogens, specific times of immunization, which would be effective for hosts as diverse as those encompassed by the claims", and therefore that it would require undue experimentation to determine the effective immunogens, immunization schedules, etc. Pursuant to MPEP §§2164.07(a)(1) and 2107(d), this §112 rejection should have been made separately from the "lack of utility" based rejection discussed in the last section.

Applicant discovered that the timing of immunization of children against childhood infectious diseases can seriously affect, for better or for worse, their chance of developing diabetes later in life. Applicant's analysis of multinational epidemiological data showed that late vaccination with BCG, pertussis and DTP vaccines increased the incidence of diabetes, and that early vaccination with BCG decreased that incidence (Example 4). Applicant postulated that a sufficiently early immunization with other immunogens would also reduce the incidence of diabetes in later life. Applicant was able to confirm this experimentally. In Example 1, Applicant showed that early immunization with plague or anthrax vaccines reduced the incidence of diabetes in NOD (non-obese diabetes-prone) mice. Further experiments, in which diphtheria, tetanus and pertussin immunogens were also used, achieved even more dramatic reductions. (Examples 2 and 3).

In the Declaration executed by Dr. Classen on July 8, 1994, further corroboration of the validity of Applicant's vaccination strategy was set forth. First, Dr. Classen showed that the incidence of diabetes could be reduced in a second animal model, BB rats. While both NOD mice and BB rats develop diabetes, their forms of the disease are immunogically distinct. Secondly,

additional epidemiological data was presented. This showed that immunization with Hemophilus influenza and smallpox vaccines affected the subsequent incidence of diabetes. Finally, it was reported that immunized MRL/MpJ-lpr mice exhibited a reduced incidence of glomeruli nephritis, and hence that the invention appeared useful in the prevention of SLE, an autoimmune disorder substantially different from diabetes.

It can be seen from both the experimental studies and the epidemiological data that a variety of immunogens -- plague, anthrax, diphtheria, tetanus, pertussis, BCG, Hemophilus influenzae and smallpox -- can affect the development of diabetes, and that early administration of plague, anthrax, anthrax + pertussis, anthrax + DPT, and smallpox immunogens can reduce the incidence of diabetes.[3]

Table VI of the 1994 Declaration compared the anthrax, plague, DT, pertussis, Hib, BCG, smallpox and MMR vaccines in terms of the nature of the vaccine. There are considerable differences. Only the BCG vaccine has been shown to contain an immunogen that cross-reacts to an autoantigen associated with type I diabetes mellitus.

Under these circumstances, it is clear that the anti-diabetic response cannot be entirely immunogen-specific, as there is no common epitope in question which could be eliciting the response. A nonspecific immune response must play an important role.

At page 12, lines 7-25 of the specification, Dr. Classen declares

> Without intending to be bound by any theory, early administration of immunogens can cause the release of lymphokines that may accelerate the maturation of the

[3] The effect of early administration of the other immunogens noted is not yet known, but is readily determined.

immune system. The immunization may act in several ways including:

A. Enhancing destruction of autoimmune prone cells in the thymus;

B. Enhancing the flow of normal T-cells from the thymus;

C. Causing peripheral elimination of autoreactive T-cells that have escaped the thymus;

D. Causing the release of interferons which prevent infection with autoimmune causing viruses; and/or

E. Causing migration of macrophages into the area of administration as in an injection site and away from an vital organ like the islet cells of the pancreas. The invading macrophages have the ability to act as antigen presenting cells and induce an autoimmune response against the vital tissue.

In contrast, the late administration of an immunogen can cause the release of lymphokines which may act as growth factors enabling autoimmune inducing cells to grown.

Lymphokines are discussed in more detail at pages 20-22 of the specification. Interferon alpha is specifically mentioned at page 21, line 19. The mechanism by which immunization with a broad range of vaccines at birth prevents diabetes can be explained through the release of alpha interferon (or other lymphokines). Alpha interferon is an molecule made by macrophages when they are activated by an immunological challenge such as an infectious organism or vaccine. Alpha interferon is routinely used to treat patients with hepatitis and other viral infections because the molecule has strong and broad antiviral activity. Alpha interferon induced by immunization at birth can help prevent diabetes through the suppression of congenital or neonatal infections, also called vertical infections. Studies from Sweden and Finland have indicated that 27% or more cases

of insulin dependent diabetes are linked to a vertical infection with Coxsackie B virus. See Dahlquist, et al., Diabetologia, 38:1371-3 (1995); Hyoty, et al., Diabetes, 44:652-7 (1995). This data is consistent with early reports linking the development of insulin dependent diabetes to congenital rubella infections. Ginspberg-Gellner, et al., Diabetologia, 27:87-9 (1984). Inhibition of these infections through nonspecific mechanisms, in particular release of alpha interferon following immunization at birth, explains why early immunization is associated with a reduced risk for developing diabetes. This mechanism of action also explains why early immunization prevents diabetes in NOD mice since a congenital viral infection has been suggested as a cause of diabetes in the NOD mouse. Gaskins, et al., J. Clin. Invest., 90:2220-7 (1992); Suenaga, et al., Diabetes, 37:1722-6 (1988); Nakagawa, et al., Diabetologia, 35:614-18 (1992).

The late administration of alpha interferon to patients has been reported to cause insulin dependent diabetes. Alpha interferon and the alpha interferon inducer Poly I:C have been shown to induce diabetes in rodents as well, explaining why late immunization induces diabetes in rodents. The induction of diabetes by late immunization also can be explained through the release of alpha interferon. The mechanism by which alpha interferon can induce diabetes include damaging the islet cells and speeding up a smoldering subclinical autoimmune disease.

The ability of interferon to modulate diabetes by two pathways, prevention through inhibiting viral infections and induction through stimulating an autoimmune response, explains the importance of timing of first immunization.[4]

---

[4] The principal reason for continuing the immunization program beyond six weeks of age is increased protection against the related infectious diseases. The preventive effect is favored by early immunization but this declines quickly with time

Potential immunogens, which could elicit, if administered early in life, an anti-diabetic immune response, are discussed in great detail at page 19, line 16 to page 20, line 17; page 24, line 11 to page 25, line 25; page 75, line 20 to page 76, line 2; page 77, lines 7-14; and original claims 18-20.

Methods of screening immunogens for suitability are discussed at length at pages 56-75, and are further exemplified by Examples 1 and 2 of the specification.

In view of the plethora of examples of potential immunogens, the diversity of the immunogens already known to affect diabetes, the plausibility of the proposed non-immunogen-specific mechanism (lymphokine release) by which the anti-diabetic effect is exerted, and the detailed presentation of the screening methodology, it is clear that one skilled in the art can, without undue experimentation, identify additional immunogens that can, by early administration, reduce the incidence of diabetes.

With regard to the issue of the determination of an effective immunization schedule, the PTO appears to have exaggerated the difficulty of this task. Applicants wish to call the Examiner's attention to the following considerations:

(a) it is routine in the art to conduct initial efficacy studies in mice and rats and to then scale-up to humans. This requires adjustment for differences in body weight, metabolism, development, etc. Such adjustments must now be deemed routine.

(b) immunization schedules are specifically suggested at

---

since by six weeks the vertical viral infection has already been firmly established. Six weeks after birth the only material effect of vaccine induced interferon is the induction of diabetes. A single dose of vaccine given at birth can prevent many more cases of diabetes than a dose of vaccine given after two months can induce diabetes. A net reduction in diabetes thus occurs even if a dose of vaccine is given both at birth and after two months.

diabetic response is satisfactory, but the anti-infectious disease effect (if sought), is unsatisfactory, the first dose may be given somewhat later. The practitioner may also wish to reduce the number of doses for economic reasons, or increase the time interval for the sake of patient convenience.

The systematic variation of a small number of quantifiable treatment parameters, so as to optimize the subject's response, is the very essence of routine practice.

With regard to the route of administration, several options are set forth on pages 33-34. For each of the conventional pediatric immunogens, one or more accepted routes exist, and these would be used unless problems (not presently expected) are encountered. Most human vaccines are given intramuscularly.

Conclusion

It is respectfully urged that for the aforestated reasons, the claims as amended are in condition for allowance. It is respectfully requested that, if the Examiner is not yet ready to allow the case, that Applicant be granted an interview prior to action.

Respectfully submitted,

BROWDY AND NEIMARK
Attorneys for Applicant

By: _____
Iver P. Cooper
Reg. No. 28,005

419 Seventh Street, N.W.
Washington, D.C. 20004
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms

f:\user19\wp\a-c\cla529us.amd